III. REMARKS

Claim Status

Claims 17-18 and 22-33 are active in the case. Claims 17-18 and 22 have been amended. Claims 1-16 and 21 have been cancelled. Claims 19-20 are withdrawn. Claims 27-33 are new.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on August 29, 2007 is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement.

Applicant is submitting herewith an IDS in proper form.

Sequence Compliance

The examiner notes that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) but does not refer to the sequences with sequence identifying numbers being recited within the specification itself.

Applicant has submitted a substitute specification containing no new matter and which adds appropriate SEQ ID NO.'s to the specification.

Applicant has also amended the sequence listing to conform to the specification, as filed.

Claim Objections

Claims 23-26 stand objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

These claims were dependent upon now cancelled claim 21. the dependency of these claims has been amended by amending claim 22 which now refers to claim 27 thus obviating this ground for rejection.

Claims Rejections - 35 U.S.C. 112, first paragraph

Claims 12-18 and 22-26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement since the claim(s) contains subject matter which was not described in the specification in that although the specification discloses SEQ ID NO:1 and 2 which meet the written description provision of 35 USC 112, first paragraph, the aforementioned claims encompass sequences that have a part thereof that comprises at least the amino acids of the C-terminal helix of apoCl and the examiner believes that none of these parts meet the written description provision of 35 USC 112, first paragraph.

Therefore the examiner concludes that only the recited sequences and not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Applicant has amended this claims to limit them to the

recited sequences, thus obviating this ground for rejection.

Claims 16-18 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Applicant has cancelled claim 16 and has amended claims 17 and 18 to depend upon claim 27 which method is now limited to peptides having the indicated amino acid sequence

Additionally, the examiner states that applicant has failed to demonstrate that the claimed pharmaceutical composition complex is effective in treating or preventively treating a mammal, which suffers from or is at increased risk of developing sepsis. Therefore, in view of the lack of support in the art, the lack of working examples commensurate in scope to the claimed invention, and the unpredictability of the generation of protective immunity, the specification, as filed, does not provide enablement for the claimed pharmaceutical composition and methods.

Applicant respectfully disagrees.

Regarding the unpredictability of the prophylactic or therapeutic effect applicant respectfully suggests the examiner errs in thinking that an immunogenic effect is required. As is explained on pages 17 and 18, the apoC1 protein (or its C-terminal part) will bind freely circulating LPS, enabling a longer exposure in the body, thereby increasing the ability of the body to develop an immune reaction to the LPS. Thus, apoC1 is not used as a vaccine, wherein antibodies need to be formed to the protein.

The binding effect of apoCl to LPS has been demonstrated in Examples 2 and 3, while the prolonged exposure time of LPS has been shown in Example 4, Further, Example 5 shows that apoCl is capable of increasing the immunogenic effect of LPS. It is believed that these experiments clearly show the *in vivo* effects of apoC1 and its potential usefulness in the prevention or treatment of sepsis.

Regarding preparation of the pharmaceutical composition which is used in the claimed method, the Examiner objects that a person skilled in the art would be unable to make the pharmaceutical composition which is used in the claimed method. This, however, is incorrect: the preparation of a pharmaceutical preparation is exemplified e.g. on pages 16 and 17 of the specification (under the heading C. Administration form and routes). Further, preparation of a pharmaceutical composition that comprises a protein is well within the skill of the artisan and does not provide an undue burden for the skilled person.

Therefore, one of skill in the art would be able to make the pharmaceutical composition and the methods for treating or preventively treating a mammal, which suffers from or is at increased risk of developing sepsis, as claimed.

Applicant respectfully requests favorable reconsideration of this ground for rejection.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 16-18 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention in that claim 16 refers to an active amount, however it is unclear what an "active" amount is or how activation of the peptide affects administration.

Claims 16 has been cancelled and claims 17 and 18 have been amened. The offending language no longer appears in the claims.

Claims 21-26 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps.

Claims 21 has been cancelled and claims 22-26 have been amended to remove the deficiency.

Claim Rejections - 35 USC § 102

Claims 12-15 and 21-26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Quarfordt et al., J. of Biological Chem. 1982. Vol. 257(24): 14642-14647.

Quarfordt et al., is a study of the effect of three human C apoproteins on the metabolism of a triglyceride emulsion with and without associated E protein and preparations of pharmaceutical compositions comprising triglyceride emulsions having apoCI.

Quarfordt et al. teach apoCI having the sequences of claims 14-15.

Applicants have cancelled claims 12-15 and 21, amended claims 22-26 and added claims 27-33 in their place.

Applicants have amended their claims to read on methods for the treatment of sepsis or septic shock in a mammal by the

administration of effective amounts of apoCI. Quarfordt et al. do not teach or suggest pharmaceutical compositions comprising human apoCl in a method for treating sepsis or septic shock.

Applicants respectfully suggest this rejection is now moot.

Claims 12-15 and 21-26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lauer et al., (J. Biol. Chem. 1988. Vol. 263(15): 7277-7286).

The examiner states that Lauer et al., teach pharmaceutical compositions comprising human apoCl.

Applicants have amended their claims to limit them to a specific use of the compositions for use in treating sepsis or septic shock. Lauer et al., do not teach or suggest pharmaceutical compositions comprising human apoCl in a method for treating sepsis or septic shock.

Applicants respectfully suggest this rejection is now moot.

Claim Rejections - 35 USC § 103

Claims 16-18 stand rejected under 35 U.S.C. 103(a)as being unpatentable over Oosten et al., (J. of Biol. Chem. 2001. Vol. 276(23): 8820-8824); and Lauer et al., (J. Biol. Chem. 1988. Vol. 263(15): 7277-7286) in view of Quarfordt et al., (J. of Biological Chem. 1982. Vol. 257(24): 14642-14647).

As stated by the examiner, Oosten et al., teach that apoE may be used therapeutically to protect against LPS-induced endotoxemia as known as sepsis; that lipopolysaccarides (LPS) are a component of gram-negative bacteria which is the primary

cause of gram-negative sepsis; that all lipoproteins bind endotoxins and that combining lipoproteins or chylomicrons with LPS before administration to rodents protects against endotoxin induced death; that emulsion models for chylomicrons target LPS and prevent the further binding of LPS, thereby showing the importance of the lipoprotein-endotoxin interactions and that administering emulsions having apoE to mammals.

However Oosten et al, do not teach administering ApoCI.

As stated by the examiner, Lauer et al., teach that human apolipoprotein Cl is closely linked to Apolioprotein E.

As stated by the examiner, Quarfordt et al., teach purifying human apolipoprotein CI (apoCl); preparations of chylomicron or emulsion models; emulsions comprising ApoE and ApoCI; administering ApoCI to rats. Table I shows the injected activity of ApoCI and that the C apolipoproteins were active within emulsions supplemented with apolipoprotein E (page 14646, col. 1).

Therefore the examiner believes it would have been prima facie obvious at the time of applicants' invention to apply the pharmaceutical emulsion composition comprising ApoE and ApoCI as taught by Quarfordt to the method for treating or preventively treating a mammal, which suffers from or is at increased risk of developing sepsis, as taught by Oosten et al., in order to therapeutically to protect against LPS-induced endotoxemia as known as sepsis.

The examiner concludes one of ordinary skill in the art would have a reasonable expectation of success by including

ApoCI within the composition of method of treatment because human ApoCI is closely linked to ApoE.

Furthermore, the examiner states ApoCI and ApoE are known to produced in emulsion chylomicron compositions; and Oosten et al., teach that emulsion chylomicron compositions target LPS and prevent the further binding of LPS.

Furthermore, no more than routine skill would have been required to include the closely linked ApoCI with the emulsions comprising ApoE when Oosten et al., teach that combining chylomicrons with LPS before administration protects against endotoxin death.

Applicant respectfully disagrees.

van Oosten et al., teaches the involvement of ApoE in sepsis. Based on the immunomodulatory action of ApoE, van Oosten et al. performed research to demonstrate that ApoE binds to the LPS and reduces the LPS response.

There was and is no reason to assume, from this reference, to expect that apoCI would also bind LPS and modulate the LPS response. ApoE and apoCI are merely two apolipoproteins, residing on the same gene cluster, with functions in lipid transport. Moreover, it appeared that apoE and apoCI have opposing effects on modulation of the LPS response: apoE reduces the response, whereas apoCl augments the response.

It has been explained in the specification why apoCI, having this augmenting effect, still is believed to be useful (paragraph [00431] of the published application).

The examiner contends that one of ordinary skill in the art would have a reasonable expectation of success by including ApoCI within the composition of method of treatment because human ApoCI is closely linked to ApoE.

The linking disclosed by Lauer et al. is not a linking of activity. As disclosed by van Oosten et al. apoE and apoCI have opposing effects on modulation of the LPS response: apoE reduces the response, whereas apoCl augments the response.

Lauer et al.'s own Table I discloses the significantly different distribution of apoCI and ApoE in various tissues.

Thus, one would not, reading of the opposing effects and the tissue differences, expect that a linking would have beneficial effects and the invention would not be obvious for a person skilled in the art from a combination of van Oosten et al. with Quarfordt et al. in light of Lauer et al.

This would only leave the objection under 35 USC §112, first paragraph, relating to the enablement of claims 16-18. Unfortunately, applicants have no further data on the usefulness of the claimed peptides for treatment of sepsis, neither negative nor positive. It is also very difficult to obtain evidence for this effect, since no animal models exist that can simulate the septic infections and from which it would be possible to predict efficacy in humans.

Favorable reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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